

TRIACETYLOLEANDOMYCIN (EVRAMYCIN) IN LYMPHOGRANULOMA INGUINALE*

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Although lymphogranuloma venereum (LGV) is a serious problem in many foreign countries, it is comparatively rare in the United Kingdom. As shown by Alergant (1957), "Somewhere between a quarter and a third of all cases of LGV reported in Great Britain are first seen"—at the Seamen's Dispensary, Liverpool. A few additional cases are treated in the other regional clinics, notably at Birkenhead, where nearly all the cases included in this survey were seen.

Although the sulphonamides, tetracyclines, and chloramphenicol are established therapeutically in roughly that order, "the contradictory results obtained by different groups of investigators leave one with a sense of confusion. The bulk of the literature describing the reaction of the disease to the sulphonamides seems to favour the use of these drugs. Therefore, although I am of the opinion that buboes and proctitis respond more rapidly to... tetracyclines, ... sulphonamides are recommended as the drugs of choice for routine therapy". (Robinson, 1952).

One disadvantage of the tetracyclines in this context lies in their anti-treponemal activity. Attempts have therefore been made to find other remedies. Two such examples reported by Alergant (1953, 1961) were respectively 2:3 dimethyl quinoxaline, 1:4 dioxide (7218), which proved too toxic, and 17,025, 5 methoxy-carbonyl-6-methyl-4-(5-nitrofuryl) 2:oxy 1:2:3:4 tetrahydropyrimidine, which showed promise.

Since the triacetyl salt of oleandomycin possesses *in vitro* activity against the virus of LGV and some of those related to it, it was decided to investigate its clinical effectiveness. Being unaware of any published report, I decided to give 250 mg. Evramycin

four times daily for 10 days, the latter being the generally accepted minimum duration of most other treatments. This system was adhered to in all except Case 8, who was treated at the Royal Infirmary, Chester. Otherwise, save for Cases 10 and 13, who after being first seen at the Seamen's Dispensary, Liverpool, were transferred at their own request, all the out-patients were seen at St. James's Hospital, Birkenhead, the in-patient work being carried out at St. Catherine's Hospital, Birkenhead.

The thirteen cases are summarized in the Table (opposite), and further details are given below:

Case 1.—This patient was infected in British Guiana, the incubation period being between 4 and 10 weeks, after several exposures. He presented with bilateral inguinal adenitis and moderate constitutional disturbance. The first LGV complement-fixation test was doubtful (1 in 20), but 3 months later had risen to 1 in 80 (the minimum diagnostic positive being regarded as 1 in 40). 3 days after triacetyloleandomycin therapy had been started, a well-developed, indurated left parafrænal sore had developed from which *T. pallidum* was identified. The Wassermann reaction was negative and the cerebrospinal fluid normal. Penicillin injections (PAM 600,000 units daily for 10 days) were at once started and within a further week the clinical picture had become normal. Since then, in late 1959, he has had two attacks of non-specific urethritis but a recent pre-marital assessment disclosed no abnormalities.

Case 2.—This patient, having contracted the disease in India 8 weeks previously, had a well-marked bilateral inguinal adenitis with malaise and pyrexia. There was also a history of an apparently untreated chancre 3 years before and the Wassermann reaction (1 in 128) and Meinicke test were both strongly positive, while the cerebrospinal fluid was normal. He was treated first with triacetyloleandomycin and subsequently with penicillin. The swelling in the glands had subsided within a week and 18 months later all was well with a negative Wassermann reaction and Meinicke test.

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Case 3.—This Indian, 7 weeks after exposure in India, had developed a left inguinal adenitis which had failed to respond to a 3-day course of sulphadiazine on board. Despite the doubtful LGV complement-fixation test, triacetyloleandomycin was given 2 weeks after the start of symptoms and there was a satisfactory recovery, after which the patient returned to India.

Case 4.—After exposure in Panama 6 weeks previously, this Spaniard had developed symptoms 4 weeks later, which were not relieved by a 3-day course of sulphadimidine on board. Having been admitted to hospital, he improved rapidly with Evramycin, but after 6 days took his own discharge as he was "now cured".

Case 5.—After being infected in Venezuela 13 weeks before, this man developed a left inguinal adenitis and had been admitted to the hospital medical ward for extensive investigation including urine analysis, blood counts, Wassermann reaction, Paul-Bunnell test, Widal test, chest x ray, marrow puncture, and finally removal of the left inguinal glands, presumably for biopsy. No diagnosis was made but two short courses of sulphadiazine

and chlortetracycline were given. 10 days later, a right inguinal adenitis appeared and my opinion was sought. He responded rapidly to treatment, and 3 months later all was well [perhaps fortunately since "... excision of inguinal nodes ... may be followed by elephantiasis of the genitals" (Canizares, 1954a)]. In a very recent examination of this patient, 18 months later, nothing abnormal was found.

Case 6.—Alone in this series, this patient did not require in-patient treatment; after a 3-week incubation period inguinal adenitis had failed to respond to a 3-day course of streptomycin injections on board. When he was first seen the adenitis was of 2 weeks' duration, but it had subsided by the fourth day of Evramycin treatment, and 3 months later the patient was clinically well. Unfortunately the blood specimen for a repeat LGV complement-fixation test was lost and he was by then *en route* to India.

Case 7.—In this instance, the disease had been contracted in India 7 weeks before the appearance of symptoms; these had lasted a fortnight and had not

TABLE
SUMMARY OF THIRTEEN CASES OF LYMPHOGRANULOMA VENEREUM

Case No.	Age (yrs)	Nationality	Inguinal Glands Affected	Frei Test	LGV Complement-Fixation Test	Complications	Other Venereal Diseases	Other Treatment	Results	Follow-up
1	21	British ..	Bilateral	+	1 in 20	None	Syphilis	None	Excellent	3 yrs
2	21	Indian ..	Bilateral	+	1 in 40	None	Syphilis	None	Excellent	18 mths
3	24	Indian ..	Left	+	Negative 1 in 20	None	None	Sulphamezathine for 2 days	Good	2 wks
4	32	Spanish ..	Bilateral	+	1 in 40	None	None	Sulphadimidine for 3 days	Improved	6 days Defaulted
5	21	British ..	Bilateral	+	1 in 40	Removal of left glands for biopsy	None	Sulphadiazine and chlortetracycline each for 4 days	Excellent	3 mths
6	30	Indian ..	Right	+	Negative 1 in 5	None	None	Streptomycin for 3 days	Excellent	3 mths
7	24	Indian ..	Bilateral	+	1 in 80	None	None	Penicillin for 4 days	Very good	4 wks
8	26	Chinese ..	Right	+	1 in 160	Deep abscess	None	None previously Later sulphadiazine for 4 days; and oxytetracycline and chloramphenicol for 4 days	No response	6 wks
9	23	German ..	Bilateral	+	1 in 40	Fluid present right side	None	None	Excellent	12 days
10	23	Danish ..	Bilateral	+	1 in 160	None	Gonorrhoea	Penicillin 600,000 units one month before	Very good	1 mth
11	23	Indian ..	Right	+	1 in 160	None	None	None	Very good	3 wks
12	32	Dutch ..	Bilateral	+	1 in 320	Fluid developed right side	None	None previously Later sulphadimidine for 6 days and oxytetracycline for 14 days	No response	6 wks
13	27	British ..	Left	+	1 in 640	Fluid already present left side	None	Sulphathiazole for 2 days and tetracycline for 4 days	Good	10 wks

responded to four injections of penicillin on board. He had headache, joint pains, pyrexia (103°F.), and malaise, as well as the inguinal adenitis. There was no response for 6 days, but the condition then completely resolved within a further 3 days.

Case 8.—My advice was sought after this Chinese patient had been admitted to a surgical ward of the Chester Royal Infirmary. He did not speak English so that the previous history is unknown. The Frei test gave a positive control reaction while the test arm reacted violently with suppuration, though Canizares (1954b) states that "the degree of positivity of the reaction bears no relationship to the severity of the infection". Despite immediate treatment his local and general condition both became aggravated and after 5 days, aspiration of the superficial glands gave no relief, the patient's temperature soaring to 105°F. The white cell count was 8,562, polymorphs 68 per cent., lymphocytes 29 per cent., and monocytes 3 per cent. Sulphadiazine was now added to the existing treatment without effect and by the 8th day, a large collection of fluid deep to Poupart's ligament required removal. A change of treatment to a combination of oxytetracycline and chloramphenicol was ineffective—and not in accordance with my advice—but rapid improvement resulted from removal of the fluid.

Case 9.—A German patient, who had acquired the infection in West Africa 5 weeks previously, presented with an elongated, matted, and tender glandular swelling of 5 days' duration in the right groin—reddening of the skin and fluctuation betokened the presence of fluid, and there was also a smaller glandular mass on the left side. By the 4th day, in contrast with the preceding case, there was a marked improvement and after the 12th day, he was fit for discharge, both swellings having completely resolved.

Case 10.—This was a second instance of an infection acquired 6 weeks earlier in West Africa. The patient, who was a Dane, had had gonorrhoea 5 weeks before, and this had responded to an injection of PAM 600,000, but he now had a marked bilateral inguinal adenitis, larger on the left, of 4 days' duration, together with considerable constitutional disturbance. After 3 days treatment with Evramycin, there was no change, but thereafter the condition improved, complete resolution of the adenitis being finally achieved 3 days after the end of the course of treatment. However, owing to two positive Wassermann reactions (1 in 128), which were later identified as acute biologic false positives, he was kept in hospital for a month.

Case 11.—This Indian patient strenuously denied intercourse, but exposure is believed to have occurred in India. He had had a painful untreated swelling in the right groin for 15 days and the deep iliac glands could be felt. After 6 days of treatment there was a marked improvement and after 10 days, complete subsidence of the swelling. When last seen 11 days later, he was fit and well.

Case 12.—This patient had acquired his infection 4 weeks previously in Nigeria. The swelling was of

2 weeks' duration and larger on the right side. Otherwise, he was well. After 2 days of treatment there was a distinct improvement which was followed by a 5-day period of no change. Both swellings then started to increase in size with fluid formation on the right. After 10 days, Evramycin was withdrawn and sulphadimidine substituted with no effect. After a further 6 days, the latter was abandoned in favour of oxytetracycline 500 mg. three times a day) for 5 days, then reduced to 250 mg. four times a day to a total of 14 days. On the 9th day of this last course of treatment aspiration was performed; the patient was discharged 2 weeks later, improved but still requiring out-patient supervision.

Case 13.—This patient developed a swelling in the left groin 11 weeks after coitus in Brazil. When he was first seen the swelling had been present for a fortnight. He was treated first with tetracycline 500 mg. three times a day for 4 days and during this time a rash appeared on his arms and legs. He then had sulphathiazole for 2 days and developed swollen wrists and pyrexia. The inguinal swelling meantime steadily increased in size.

Examination.—There was a fluctuant swelling over the enlarged left inguinal glands, and a fading rash on the thighs, legs, and forearms suggestive of erythema multiforme. The right wrist joint was slightly swollen. The patient looked ill. Sulphonamides were withdrawn, he was admitted to hospital, and Evramycin was started the following day, by which time his general condition had worsened and both wrists were swollen. After 2 days, all constitutional signs and symptoms had disappeared except the swollen inguinal glands, and these were smaller though with some residual fluid. The control reaction of the Frei test was strongly positive as well as the test proper.

Treatment was stopped after 10 days, but aspiration of the fluid was required the next day and again 4 days later, when 10 ml. and 5 ml. of sterile pus were obtained. Slight oozing of clear fluid continued for a further 10 days and then ceased spontaneously, though a steadily diminishing residual thickening persisted for some time. This occasioned the administration by a colleague of a second course of Evramycin for 4 days. It is doubtful, however, if this was really necessary. The patient now complained of diarrhoea, and 3 days after this second course a severe generalized urticarial rash for which there was no obvious cause appeared and lasted for a week. It was deemed inadvisable to give the patient any more Evramycin, to test whether it was responsible or not. The patient was finally discharged after 8 weeks in hospital, and 6 months later was still well.

Discussion

The outcome in eleven of the above thirteen cases was satisfactory and in only one were any toxic reactions noted. Csonka (1959) reported slight diarrhoea in one case out of twelve, and Willcox (1959), in a larger series of 100, had three patients who complained of "rectal burning, soreness, or

irritation". In general practice, with treatment courses not exceeding 5 days, Read (1961) had five cases of diarrhoea out of 23 who were not given Vitamin B complex and only one out of 31 who did receive Vitamin B complex. Shubin, Cohen, and Rosen (1959) reported nineteen cases with "nausea, vomiting, and diarrhoea" out of a series of 230. These untoward effects appear to be the only ones reported after courses of treatment not longer than 2 weeks. All my thirteen cases received Vitamin B complex.

Loughlin, Aleindor, and Mullin (1959) reported a series of 27 cases of lymphogranuloma venereum treated with triacetyloleandomycin (23 males and four females, two of the latter with proctitis). The dosage used was 1 g. twice daily for 5 days; in short, twice as much for half as long as in the present series. This is surprising as periods of treatment ranging from 10 to 14 days, irrespective of any particular remedy, are now regarded as standard. Not surprisingly, the course had to be repeated in eleven cases and was then "uniformly effectual". These authors state that with the first course "partial regression of the lymphadenitis was generally apparent by the fourth or fifth day . . . even when there was fluctuation of the glands. Regression of the inflammatory and ulcerous lesions of proctitis was noted by the fifth or sixth day of treatment". There were no toxic reactions.

Although it is too early to make any spectacular claim, especially in view of the characteristics of LGV which make the relative assessment of different therapies so difficult, there is undoubtedly a strong case for persevering with Evramycin in order to evaluate more conclusively its place in the treatment of this troublesome complaint, particularly as it has no masking action in syphilis.

Summary

An account is given of thirteen cases of lymphogranuloma venereum treated with triacetyloleandomycin (Evramycin). In only two cases was there complete treatment failure. In one other case primary syphilis appeared after the start of treatment. Only one patient suffered toxic reactions. It is concluded that there is a strong case for further trials of this medication.

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Traitement du lymphogranulome inguinal par l'Evramycine

RÉSUMÉ

Ou décrit 13 cas de lymphogranulome inguinal traités par la triacetyloleandomycine (Evramycine). Le traitement n'échoua complètement que dans deux cas. Dans un autre cas la syphilis se déclara après l'inception du traitement. Un malade présenta des réactions toxiques.

Ou constate qu'il faut entreprendre de nouveaux essais de ce médicament.